Complexity analysis of spontaneous brain activity in mood disorders: A magnetoencephalography study of bipolar disorder and major depression

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Abstract

Background and purpose: The lack of a biomarker for Bipolar Disorder (BD) causes problems in the differential diagnosis with other mood disorders such as major depression (MD), and misdiagnosis frequently occurs. Bearing this in mind, we investigated non-linear magnetoencephalography (MEG) patterns in BD and MD.

Methods: Lempel-Ziv Complexity (*LZC*) was used to evaluate the resting-state MEG activity in a cross-sectional sample of 60 subjects, including 20 patients with MD, 16 patients with BD type-I, and 24 control (CON) subjects. Particular attention was paid to the role of age. The results were aggregated by scalp region.

Results: Overall, MD patients showed significantly higher *LZC* scores than BD patients and CONs. Linear regression analyses demonstrated distinct tendencies of complexity progression as a function of age, with BD patients showing a divergent tendency as compared with MD and CON groups. Logistic regressions confirmed such distinct relationship with age, which allowed the classification of diagnostic groups.

Conclusions: The patterns of neural complexity in BD and MD showed not only quantitative differences in their non-linear MEG characteristics but also divergent trajectories of progression as a function of age. Moreover, neural complexity patterns in BD patients resembled those previously observed in schizophrenia, thus supporting preceding evidence of common neuropathological processes.

Keywords: Bipolar disorder; Lempel-Ziv Complexity; Magnetoencephalography; Mood disorders; Psychosis Continuum.

1. Introduction

Bipolar disorder (BD) is a chronic and debilitating disease characterized by "abnormal" shifts of mood and energy. The term "bipolar" refers to recurrent episodes that are polar opposite on a continuum between elevated and depressed mood [1]. Currently, there is no objective marker for BD and diagnosis relies on clinical criteria such as the Diagnostic and Statistical Manual of Mental Disorders– DSM-5 [2]. Neurophysiological features are potential candidates for the elucidation of a BD-related biomarker since disturbances in the behavior of the oscillatory patterns may indicate aberrant brain function [3]. Most of the resting state EEG studies of BD revealed a pattern of increased low-frequency and decreased alpha activity [4, 5]. The decrease of alpha activity was further highlighted by Basar's group [6, 7]. The authors claimed that, although such decrease is shared by schizophrenia (SZ) and BD patients, it is quantitatively greater in the latter, representing a marker of the disease. Additional findings confirmed this pattern of increased low-frequency activity but pointed out abnormally slow beta activity in BD and SZ patients that, according to Narayanan et al.'s [3] point of view, might indicate a common endophenotype for both disorders. However, Venables and coworkers [8] failed to find an abnormal beta or even the typical pattern of increased low-frequency activity in BD.

Investigations using spectral analysis depicted a quite unspecific picture of BD since increased low-frequency and decreased high-frequency activity is a feature not only shared with SZ but also with Alzheimer's disease and mild cognitive impairment [9-12]. Hence, traditional analysis procedures have been challenged by new methods derived from non-linear dynamics analysis and information theory that can reveal features not available to other techniques. Complexity and entropy estimates are good examples of this new arsenal of analysis methods. In particular, parameters of EEG or

Magnetoencephalography (MEG) complexity usually estimate the predictability of brain oscillations (with more “unpredictable” signals yielding higher complexity scores) and/or the number of independent oscillators underlying the observed signals [13]. With regards to BD investigations, Glenn et al.[14] and Gottschalk et al.[15] used dimensional analysis and approximate entropy to analyze mood variations over time, finding contradictory results of increased or decreased complexity. Thomasson and coworkers [16] analyzed EEG by means of entropy estimates in a 48-hour cyclic BD patient, and found that the signal complexity increased during manic phases and decreased during depressive mood. Bahrami et al. [17] also found that dimensional complexity was increased during manic episodes. Finally, a very recent multiscale entropy analysis of fMRI signals revealed decreased complexity in BD and SZ [18]. The observed contradictory results might be explained by discrepancies in the inner properties of the selected analysis procedure, and also by the diversity of analyzed signals. Some complexity estimators are more sensitive to certain characteristics of brain signals [19]. Therefore, it is convenient to select those estimators that do not require a large amount of data, and stationary or noise-free time series, as it is usually the case for EEG and MEG. It is also important to note that MEG measures direct neural activity as compared with MRI-derived estimates.

Lempel-Ziv complexity (*LZC*) meets these characteristics and has been successfully used in the investigation of psychiatric disorders. For instance, Li et al.[20] found that *LZC* values were more sensitive than conventional spectral measures to discriminate SZ and psychotic depression patients. Previous studies by our group using MEG technology [21-23] demonstrated that some neuropsychiatric disorders can be characterized by specific patterns of *LZC* variation. Importantly, although variations among diseases existed, they all shared a common characteristic: a rupture of the

"normal" increase of complexity scores as a function of age [24, 25] that was recovered with clinical improvement [23].

The present study was designed to investigate non-linear MEG patterns in BD, and more precisely, to assess whether BD patients also exhibit the above described rupture of the "normal" increase of complexity scores as a function of age. Contrary to the vast majority of precedent neurophysiological studies that compared BD and SZ, we decided to investigate *LZC* patterns in BD and major depression (MD). Such decision was based on the fact that both diseases share some key characteristics as mood disorders and misdiagnosis frequently occurs. As a consequence, it might be intuitively hypothesized that complexity scores in BD may exhibit a similar behavior as compared with MD patients. Nevertheless, previous studies (see for example [26]) reported quite distinct MEG patterns in both clinical conditions, and therefore such intuitive hypothesis might be questioned.

2. Methods

2.1 Subjects

The sample analyzed in this study included three groups. a) 20 patients who fulfilled the criteria for MD without any diagnosis of comorbid disorders, henceforth called MD group. Patients were moderately to severely symptomatic and remained free of antidepressant treatment for a 3-week period prior to the MEG scan. For a complete description of this group see [23]. b) 16 patients who fulfilled the criteria for bipolar disorder type I (i.e., patients who presented a full manic episode) without any diagnosis of comorbid disorders, henceforth called BD group. BD patients were euthymic at the moment of MEG scans but under pharmacological treatment with lithium salts (70%) or valproate (30%). Notably, BD patients had no previous episodes of psychotic symptoms during the acute phases of the disease. c) 24 Control (CON) subjects.

Patients' inclusion criteria for BD and MD were based on the Structured Clinical Interview for DSM-IV-TR Axis I Disorders (SCID) [27]. Only patients underwent SCID evaluation. Subjects with a history of head trauma, drug abuse (including alcohol dependence) or neurological diseases were excluded from the study. The average age of the MD group was 47.5±13 (mean ± standard deviation, SD; age range 26 to 66 years) and it was composed of eight males and twelve females. As for the BD group, the average age was 46.4±18.7 years (mean ± SD; age range 21 to 69 years) and it was composed of eight males and eight females. Finally, the 24 control volunteers (12 males and 12 females) had no history of psychiatric disorder. Their average age was 41.25±13.3 years (mean ± SD; age range 24 to 64 years). The differences in age between the MD and CON and the BD and CON groups were not significant (*p*-value=0.12 and 0.33, respectively, Student's *t*-test).

The regional ethics committee for clinical research approved this investigation and all participants gave their informed consent to participate in this study.

2.2 MEG acquisition

In this study, a 148-channel whole-head magnetometer (MAGNES 2500 WH, 4D Neuroimaging) located in a magnetically shielded room at the "Centro de Magnetoencefalografía Dr. Pérez-Modrego," Spain, was used to acquire the MEG recordings. Resting state brain activity was recorded while each volunteer was laying on a patient bed, awake and with eyes closed. For each subject, five minutes of MEG background activity were recorded at 678.19 Hz with a 0.1–200 Hz hardware bandpass filter. The MEG equipment decimated each 5-min recording by a factor of four using a second-order Butterworth IIR anti-aliasing filter, which was applied in both forward and reverse directions with cut-off frequency at 76.30 Hz (45% of the final sampling frequency: f_s = 169.54Hz). Finally, the recordings were transferred to a computer as

ASCII files.

A visual inspection assisted with an amplitude thresholding method [28] was used to select the MEG epochs of 10s with reduced ocular activity for further analysis, blind to the subject's diagnosis. The average number of epochs available for analysis in each group (given as mean ± SD) is 28.8±1.36, 27.7±3.8, 28.6±2.0 for MD, BD and CON, in that order. Finally, a 560th order FIR filter designed with a Hamming window was utilized to digitally filter the MEG epochs between 1.5Hz and 40Hz to reduce the impact of muscular, ocular and power line artefacts in the analyses.

2.3 Lempel–Ziv complexity calculation

Formally, *LZC* is a non-parametric metric which counts the number of distinct substrings and their rate of recurrence along a given time series. The higher the number of substrings, the higher the *LZC* value, which is then associated with more complex data [29]. *LZC* requires the signal to be discretized into a small number of symbols (often just two) according to a predefined rule. To do so, in this study, we followed the common practice of binarizing the time signal using its median as threshold due to its robustness to outliers [30, 31]. Then, the sequence of symbols is scanned from left to right. A complexity counter $c(N)$ is increased by one unit every time a new subsequence of consecutive symbols appears [31]. However, this would result into a complexity measure dependent on the signal length. To avoid this problem, the value of the counter can be normalized dividing it by $b(N) = N/\log_a(N)$, with a indicating the number of symbols used in the discretization. The normalized *LZC* can be computed as $LZC(N) = c(N)/b(N)$. It is bounded between 0 and 1.

2.4 Data reduction and statistical analyses

In this study, *LZC* features were computed for each 10s epoch, channel and subject in the three groups (MD, BD and CON). For each channel and subject, the results were

averaged across epochs. We assessed the variability in the *LZC* results across epochs by computing the coefficient of variation (CV, standard deviation divided by the mean) for each subject and channel. Then, the 148 MEG channels were grouped into five regions (Anterior, Central, Left, Right, and Posterior) for reducing the dimensionality of the results. Afterwards, the mean value was computed for each region following successful previous approaches [21, 22]. Accordingly, five MEG variables were submitted to statistical analyses per subject: Anterior_*LZC*, Central_*LZC*, Right_*LZC*, Left_*LZC*, and Posterior_*LZC*.

Considering our particular interest on age effects, we examined the differences between groups' means and standard deviations for statistical significance with a one-way analysis of variance with Age factor as covariate (ANCOVA). Chi-square tests of homogeneity were applied to evaluate group differences in Gender. The relationship between age and *LZC* scores was investigated by means of linear regression analyses in the three groups within each of the five regions. Multiple comparisons were corrected by means of Bonferroni's method. Finally, we also fitted Logistic Regression models to evaluate the contribution of *LZC* variables and Age to the explanation of MD vs. BD and BD vs. CON group differences. The Logistic Regression modeling followed Hosmer and Lemeshow's [32] recommendations. Authors suggested that the variable selection process should begin with a careful univariate (i.e. one by one) analysis of each potential prognostic variable. Any variable whose univariate test has a p-value < 0.25 should be considered as a candidate variable for the multivariate model. Such a conservative screening criterion was based on the notion that more traditional levels (such as 0.05) might fail to identify variables with a potential biological importance. Once candidate variables were identified by the univariate analysis, they were all

submitted to a stepwise multivariate analysis in order to select those that should be included in the final model.

Statistical analyses of data were carried out using Excel, SPSS 22 software and Matlab. The computation of *LZC* was carried out in Matlab**.**

3. Results

3.1 Gender effects

Gender distribution did not show statistically significant differences among groups (p= 0.548 for MD vs. BD, and p=0.507 for BD vs. CON). In addition, gender did not exert a significant effect on MEG variables when its influence was assessed within each group or across all groups. This was assessed with a *t*-test comparing *LZC* values between males and females.

3.2 ANCOVA analyses

Table 1 illustrates *LZC* scores on each region for MD, BD and CON subjects. Results indicated that Diagnosis and Age factors did not exert a significant individual effect on *LZC* scores, but the Age x Diagnosis interaction was significant in all sensor groups (all p values < 0.05) with the exception of Anterior_*LZC* (p= 0.071) and Posterior_*LZC* (p= 0.194). Post-hoc pair-wise comparisons indicated that MD patients showed significantly higher *LZC* scores as compared with BD patients in Right_*LZC*, Left_*LZC*, and Central_*LZC* (all p values < 0.05). No significant differences emerged in the MD vs. CON comparison.

######Insert Table 1 about here######

Table 2 summarises the CV for the LZC scores on each region for MD, BD and CON subjects. It can be seen that the variability in the results is small in comparison with their average values.

######Insert Table 2 about here######

3.3 Linear regression analyses

Considering ANCOVA findings, linear regression analyses were carried out to further explore the relationship between age and *LZC* scores on each group of sensors. Results showed no significant relationship within MD patients (all p-values > 0.238), while regression coefficients showed a positive tendency within CON subjects in all regions that reached the significance level in Left_*LZC* and Central_*LZC* sensor groups (p-values < 0.05). These findings indicated a significant increase of *LZC* scores with older age (see Figure 1) in CON subjects. In contrast, *LZC* scores were negatively correlated with age for BD patients and such tendency was statistically significant in the Right_*LZC* sensor group (p< 0.05).

Regression data, together with ANCOVA analyses, suggested the most sensitive variables in order to differentiate MD, BD, and CON groups. Overall, MD patients showed the highest *LZC* scores, especially when compared with the BD group, (see Table 1 and Figure 1) but those scores remained stable with age. On the other hand, complexity scores tended to increase as a function of age in CONs, while BD patients exhibited an opposite tendency. This strong dependence on age implies that BD's and CON's regression lines "cross" at certain age points. The "crossing-points" were 41 years of age for Anterior, 37 years for Central, 34 years for Left, 36 years for Right and 31 years for Posterior sensor group. A key consequence of these results is that, even assuming a substantial overlapping in the younger portion of the sample (see Figure 1), younger BDs exhibited a tendency to higher *LZC* scores than younger CONs. The

opposite tendency was more evident in the older portion of the sample, where BD patients showed the lowest *LZC* values. The MD vs. BD comparison displayed a quite different situation. Here the "crossing points", when existent, appeared very early and the regression lines diverged with MD patients exhibiting overall higher scores (see Figure 1). Those "crossing-points" were 23 years of age for Anterior, 22 years for Central, and 23 years for Right sensor groups. This implies that *LZC* values diverged in MD and BD from the beginning of the sample's Age distribution. As a logical consequence, the discrimination of MD and BD patients may be an easier task than the discrimination of BD patients and CONs.

######Insert Figure 1 about here######

3.4 Logistic regression analyses

Two types of predictor variables were considered: Age, which was included by default in the models, and the *LZC* scores obtained in each sensor group. The variable selection process began with a univariate analysis of each *LZC* variable. With regard to the MD vs. BD modelling, all *LZC* variables (all p-values < 0.05; p-value of 0.009 for Right_*LZC*) demonstrated a significant predictive power in the univariate analyses. Among those, a multivariate stepwise procedure selected Right_*LZC* (p= 0.011) as the final candidate. The inclusion of Age or the Right_*LZC* x Age interaction did not yield any significant improvement on the model, confirming that the MD vs. BD discrimination is not so dependent on Age effects, since complexity scores remain higher in the MD group along the age distribution. The Nagelkerke R^2 goodness of fit statistic was 0.345, indicating that about 35% of the variation in the dependent variable (MD vs. BD patients) was explained by the logistic model. Finally, 75% of the MD

patients and 68.8% of the BD patients were correctly classified with a 0.5 cutoff point. The total classification accuracy of the model was 72.2%.

An identical procedure was carried out for the BD vs. CON discrimination. In this case, three variables Left_*LZC* (p= 0.168), Right_*LZC* (p= 0,154), and Posterior_*LZC* (p= 0.219) demonstrated a predictive power in the univariate analyses. The multivariate procedure again selected Right_*LZC* as the final candidate. This is an expectable result since Right_*LZC* is the region where BD patients exhibit lower scores as compared with CONs and also with MD patients. Following the operation as suggested by Hosmer and Lemeshow [32], the final model which optimizes its discriminating capability contained Age (p= 0.04), Right_*LZC* (p= 0.07), and Age x Right_*LZC* (p= 0.043). The Nagelkerke R^2 goodness of fit statistic was 0.243, indicating that only about 25% of the variation in the dependent variable (BD vs. CON) was explained by the logistic model. This relatively low explanatory capability was also evidenced by the sensitivity results. With a 0.55 cutoff point, the model's sensitivity was low (43.8% of correctly classified BD patients) but the specificity was markedly high (91.7% of correctly classified CONs). The total classification accuracy was 72.5%.

Considering the relatively low sensitivity of the previous model, a new analysis was accomplished. The fact that regression lines of BDs and CONs tend to show an intersection point at certain Age value may indicate that Age might exhibit a not totally linear behavior that could be revealed by means of a logarithmic transformation. A new model, containing Right_LZ, Age and Right_LZ x ln(Age) was fitted. All the predictor variables were significant with p values < 0.05, and the Nagelkerke R^2 goodness of fit statistic was 0.317 indicating that about 30% of the variation in the dependent variable was explained by the new model. With a 0.45 cutoff point, the new model showed identical high specificity (91.7% of correctly classified CONs) but improved sensitivity

(62.5% of correctly classified BD patients).The total classification accuracy was 80.0%. For explanatory purposes, it is important to note that ages of incorrectly classified BD patients were not randomly distributed. Ages of the misclassified patients ranked at the middle values of the Age distribution (34-50 years, where regression lines tend to cross). The sensitivity improvement of the model containing the logarithmic term is due to the fact that more patients with ages at the extrema of the Age distribution are now correctly classified.

4. Discussion

As noted in the Introduction, BD and MD share some key clinical characteristics as mood disorders. This intuitive notion has been confirmed by several neuroimaging studies that reported common abnormalities affecting limbic, subcortical and prefrontal regions involved in mood regulation (for a review see [33, 34]). Notwithstanding, a previous MEG study [26] comparing these clinical conditions reported distinct neuropathological patterns that have been confirmed by our present findings on neural complexity profiles. Such findings indicated that BD and MD showed not only quantitative differences in terms of complexity values but divergent trajectories of complexity progression as a function of age. MD patients exhibited higher values that remained stable as age increased. On the other hand, younger BD patients displayed slightly higher complexity values than CONs but those values tended to linearly decrease as a function of age, and as a result older patients exhibited lower values than their healthy coetaneous. Consequently, BD's and CON's regression lines crossed at certain age points, while BD and MD patients' trajectories diverged very early, indicating that neural complexity is characterized by a quite different behavior in these pathologies.

Some previous studies heralded current results. The profile of increased neural complexity in MD was previously reported by Li et al. [20] and Thomasson et al. [35]. Notably, Mendez et al.'s [23] and Thomasson et al.'s [35] results revealed the pathological nature of that increase since a successful treatment decreased complexity levels in MD patients. However, although MD and BD cases displayed a similar increase at younger ages in the current study, the progression of complexity patterns with age in our BD patients virtually mirrored that previously found in SZ. Fernandez et al. [22] demonstrated that *LZC* scores of SZ patients exhibited the same pattern now observed in BD: higher values than controls at younger ages that progressively decreased (including the existence of "crossing points" at ages around 35-50 years) resulting in older SZ cases showing lower values than controls. This evident parallelism strongly supports the presence of shared neuropathological processes in both diseases. In this vein, the mechanisms underlying complexity variations in mental illnesses have been recently discussed in some monographies [36-38]. Fernandez et al. [36] claimed that SZ patients might present a "natural" tendency to augmented neural complexity due to a disorganized or irregular (i.e. less predictable) spiking activity. Following this reasoning thread, very recent investigations demonstrated that neural firing patterns and network activity may be also more irregular in BD due to some abnormalities in fast synaptic inhibition and ion channels regulation [39-41]. An additional factor that may contribute to a progressive complexity decrease is the existence of a disconnection syndrome [42]. This idea was posed in the classical studies by Karl Friston [43] and had an important influence on neural complexity research. Investigations on BD [44-47] pointed out the presence of abnormalities in the white matter microstructure that led to a loss of connectivity. Those white matter abnormalities are present very early in the disease and progress after the first symptomatic episode [48]. A recent investigation by

our group [49] demonstrated that loss of connectivity reduces complexity not only in simulation studies [50] but more importantly in brains in vivo, since a reduced integrity of white matter tracts significantly correlated with reduced complexity scores. Importantly, our neural complexity results are in line with a recent review that highlighted some features observed in temporal complexity estimators within BD patients. Those features were proposed as markers of a neurodevelopmental disorder, thus showing a new parallelism with SZ [51].

The majority of studies investigating common features in BD and SZ include bipolar type I cases that have a higher risk of presenting psychotic symptomatology. Such a fact raises the question of whether shared cognitive, anatomic or functional characteristics are caused by a common and central underlying mechanism or rather by the influence that, for instance, delusional activity exerts on brain functioning. In this regard, Lee et al. [52] and Raghavendra et al. [53] demonstrated that complexity estimates such as correlation and fractal dimensions were specifically elevated in patients with active delusional and hallucinatory activity. This is to say that only those BD patients presenting positive psychotic symptomatology could be expected to exhibit increased neural complexity. Our current results indicated this is not the case. BD patients in our sample were symptom-free at the time of MEG recordings and had no previous history of delusional or hallucinatory activity during acute phases. Thus, the pattern observed in our younger patients does not rely on the presence of psychotic symptoms.

On the other hand, it is important to consider that the complexity values most sensitive to distinguish BDs from MD or CON subjects were localized within the right sensor group. In addition, age effects were more prominent within this region. Previous studies reported a certain right-hemisphere lateralization problem in BD. Such notion was supported by EEG evidences of “additional right hemisphere activity” in Clementz et

al.'s [4] classical study, by the MRI evidences of specific right-hemisphere white matter abnormalities [54] and functional disturbances [55], or by very recent studies of lateralization of function in euthymic BD [56]. Overall, these investigations reinforce to some extent the early assertion by Flor-Henry [57] of a right-hemisphere dysfunction in BD although the actual situation is probably better represented by a more complicated scenario.

Concluding this discussion, it is worth noting that our study was limited by the relatively small sample-size, its cross-sectional rather than longitudinal design to investigate age effects, and the uncontrolled medication influence. In fact, medication effects have been assumed to mediate the progressive complexity changes observed in our BD sample. Additionally, it is important to mention that other innovative approaches, such as cross-correlation and connectivity analyses of sensor pairs, can be used to identify MEG or fMRI markers for mental disorders [58-60]

5. Conclusions

Despite the limitations of this study, our results showed two important findings:

1) Although MD and BD share some important clinical characteristics, their patterns of neural complexity, especially those related to their progression with age, appeared as clearly divergent. 2) On the contrary, neural complexity patterns in BD patients resembled those previously observed in SZ [25]. The degree of coincidence is so remarkable that it is intriguing to propose this pattern of complexity progression with age as a new example of a common neuropathological process in BD and SZ. However, a specificity related to the localization of the most affected brain regions exists. Our results pointed to a lateralized right-hemisphere signature in BD.

Acknowledgements

To all the patients and controls who participated in this study and to their families.

Funding Source

This study was partially supported by funding from Organon S.A. Spain. The sponsors had no role in the design or conduct of the study, in the collection, management, analysis, or interpretation of the data; or the preparation, review, or approval of the manuscript.

None of the authors have potential conflict of interest to be disclosed.

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Table and Figure Legends

Table 1. Mean value of *LZC* features in MD, BD and CON groups for each region.

Table 2. Coefficient of variation (CV) of the *LZC* features in MD, BD and CON groups for each region.

Figure 1. Linear regression of the *LZC* results (y axis) versus age (x axis) in the five regions for MD (blue circles), BD (red triangles) and CON (black crosses) subjects. Regression lines are represented by blue solid lines for MD group, red dashed lines for patients with BD disease and black dotted lines for the CON group. MD patients and CONs showed a significant tendency to increase *LZC* scores as a function of age, while BD disease showed an opposite tendency. Sample size, MD = 20, BD= 16 and CON = 24.

Table 1

	Group	Region				
		Ant.	**Cent.**	**Left**	**Right**	**Post.**
LZC	**MD**	0.73	0.74	0.71	0.71	0.70
	BD	0.68	0.70	0.64	0.64	0.65
	CON	0.69	0.72	0.67	0.67	0.67

Table 2

	Group	Region				
		Ant.	**Cent.**	**Left**	**Right**	**Post.**
CV of *LZC*	**MD**	0.0331	0.0301	0.0365	0.0358	0.0361
	BD	0.0511	0.0427	0.0521	0.0524	0.0490
	CON	0.0411	0.0360	0.0430	0.0432	0.0432